Remarks

Claims 1, 5-8, 13-17, 19, 20, 23 and 24 are pending. New claims 25-26 are added herein (see below).

Claims 1, 6-8 and 14-15 are amended herein. Support for the amendments can be found throughout the specification, such as but not limited to page 4, lines 8-20; page 13, lines 15-20; page 15, lines 4-10; and Figs. 1-6.

No new matter is added herein. Reconsideration of the subject application is respectfully requested.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1, 5-8, 13-17, 19-20 and 23-24 are rejected under 35 U.S.C. 112, first paragraph as allegedly not being enabled by the specification. Applicants respectfully disagree with this assertion.

At the outset, the Office action confirms that the specification is "enabling for a method for treating major depression or dysthymia in a subject, the method comprising selecting a subject diagnosed with major depression or dysthymia using specific criteria for major depression or dysthymia the subject also has frown/glabellar lines and administering to a subject 30 to 50 unit equivalents of botulinmum toxin to a corrugator or procerus muscle and wherein the subject is treated with a therapeutically effective amount of a serotonin specific reuptake inhibithors (SSRIs)." The Office action further provides reference to specific sections of the specification (page 4 and Examples 1-4 found on pages 17-18) that provide support for treating subjects with major depression or dysthymia as well as frown/glabellar lines.

New claims 25-26 are directed to these embodiments. Allowance of claims 25-26 is respectfully requested.

However, the Office action alleges that the specification does not reasonably provide enablement for a method of treating major depression or dythymia in any subject, the method comprising selecting a subject diagnosed with major depression or dysthymia using specific criteria for major depression or dysthymia , and administering to the subject 30 to 50 unit

equivalents of botulinmum toxin to a corrugator and/or procerus muscle and wherein the subject is treated with a therapeutically effective amount of a serotonin specific reuptake inhibithors (SSRIs)." Specifically, Office action alleges that claimed methods are not enabled for subjects without frown/glabellar lines. The Applicant respectfully disagrees.

In support of this assertion, the Office action asserts that the prior art teaches that the effects of botullinum toxin are unpredictable. Specifically, the Office action cites Brenner (*Southern Medical Journal* 92: 738, 1999). Brenner describes that Botulinum toxin A prevents the release of acetylcholine at the neuromuscular junction and produces temporary paralysis of a facial muscle. Brenner describes a case history, which provides information on one subject, a 44-year old woman. This woman does not present with any psychiatric disorder, and has not been diagnosed with depression or dysthymia. Specifically, Brenner describes this woman as "satisfied with her work and home situation," and states that she has "no significant periods of anxiety or depression," has "no history of eating disorders," and is not taking any medication." Brenner does not describe a psychiatric evaluation at the time of treatment with botulinum toxin. Brenner describes the administration of botulinum toxin for cosmetic purposes to forehead rhytides. As indicated in the declaration of Dr. Finzi, this injection is likely into the muscles of the forehead (the frontalis muscle). Two weeks after receiving an injection of botulinum toxin, the woman reports anxiety, depression, restlessness, insomnia, depersonalization, and an inability to concentrate. She is treated with psychotropic drugs. Following treatment with psychotropic drugs, she is diagnosed with difficulties with emotional control using clinical criteria. Brenner concludes that the loss of muscular activity might have triggered an anxiety response in woman who did not have significant anxiety or depression. Brenner suggests that it may be beneficial to perform psychiatric tests prior to administering botulinum toxin, to identify those normal subjects that might suffer a loss of emotional control following cosmetic treatment.

The methods used by Brenner et al. differ substantially from the claimed methods, in the following elements:

1. Brenner et al. do suggest, nor render obvious, the selection of subjects with a psychiatric disorder consisting of major depression or anxiety, but describes the treatment of a subject without any psychiatric disorder.

2. Brenner et al. teach administering to the subject botulinum toxin into forehead rhytides. As discussed in the Declaration of Dr. Finzi, this administration is likely to the

frontalis muscle. Brenner does not describe administration of 30-50 Unit equivalents of Botulimum toxin to a corrugator supercilii and/or the procerus muscle to cause paralysis of the corrugator supercilii and/or the procerus muscle;

3. Brenner does not describe administering SSRIs.

In effect, the Office action is alleging that the specification is non-enabling based an adverse effect seen in one patient, who did not have a psychiatric disorder (as compared to a subject with a psychiatric disorder consisting of major depression, dysthymia or primary intermittant anxiety) who is treated using a different administration (into the frontalis muscle as compared to the corrugator supercillii or the procerus muscle) and is treated only with a single agent (without adminstration of SSRIs). This is akin to alleging that a non-menopausal woman, who is given oral estrogen (perhaps to clear up her skin) and then has adverse side effects, such as weight gain, negates the utility of an estrogen ring in menopausal woman for the treatment of vaginal dryness. This is simply not an appropriate standard.

For comparison, data is presented in the accompanying Declaration of Dr. Finzi under 37 C.F.R. § 1.132 (hereinafter the "Declaration"). As disclosed in the Declaration, a 38 year old female with a history of depression was selected for treatment with botulinum toxin. She was diagnosed with a psychiatric disorder consisting of major depression. Her BDI-II score prior to treatment was 31 and she did not have frown or glabellar lines. Following selection, 30 to 50 unit equivalents of Botulinum toxin was administered to a corrugator supercilii and procerus muscle to cause paralysis of the corrugator supercilii and the procerus muscle. Her ability to frown was decreased following treatment. In addition, her depression was treated. Two months after treatment, her BDI-II score was 2. This provides evidence that a subject without frown or glabellar lines, who is treated with botulinum toxin to a corrugator supercilii and procerus muscle would experience an improvement in her depresssion without the adverse effects described by Brenner in one subject without a psychiatric disorder.

Thus, there is no basis for the assertion in the Office action that the claimed methods would not work in subjects without frown or glabellar lines. Moreover, the Applicant has obtained additional evidence that the claimed methods are effective in all subjects including

subjects without frown or glabellar lines. Results from two patients are presented in the accompanying Declaration. This Declaration provides two case histories of the successful treatment of two subject using the claimed methods; these subjects did not have frown and/or glabellar lines. The following *Wands* analysis is provided:

(1) The breadth of the claims:

The claims are limited to methods for treating major depression or dysthymia in a subject. These methods include selecting a subject diagnosed with a disorder consisting of major depression or dysthymia using specific clinical criteria for major depression or dysthymia, and administering to the subject a specific dose, namely 30 to 50 unit equivalents of a Botulinum toxin to defined muscles, namely a corrugator supercilii and/or procerus muscle to cause paralysis of the corrugator supercilii and/or the procerus muscle. The subject is also treated with a therapeutically effective amount of a selective serotonin reuptake inhibitor (SSRI). The treatment results in decreasing the ability of the subject to frown and treating the disorder consisting of major depression or dysthymia in the subject. The scope of the claims is limited.

(2) The nature of the invention

The invention is defined methods for treating a disorder consisting of major depression or dysthymia. Subjects are diagnosed using specific clinical criteria for major depression or dysthymia. These methods utilize specific therapeutic agents (30 to 50 unit equivalents of a Botulinum toxin and SSRIs) and routes of administration (the botulinum toxin is administered to the corrugator supercilii and/or the procerus muscle).

(3) The relative level of those of skill in the art

The Office action confirms that the level of those of skill in the art is high.

(4) The amount of direction or guidance presented

A considerable amount of guidance is provided in the specification. Botulinum toxin is described on pages 10-13. The identification of subjects to be treated using the claimed methods is disclosed on pages 13-14. Techniques for administration are

described on pages 14-16, and schematic diagrams illustrating the techniques are provided in the figures. The adminstration of additional modalities, such as SSRIs is described on page 16. A number of working examples are presented in the Examples section. Thus, there is a considerable amount of guidance provided by the specification.

(5) The state of the prior art

Clinical methods for identifying subjects with psychiatric disorders, such as major depression, dysthymia and intermittent anxiety are established. The administration of botullinum toxin readily can be performed by a skilled clinican, such as by a physician.

(6) The predictability of the art

Contrary to the assertions made in the Office action, the effects of administering botulinum toxin to subjects with a psychiatric disorder consisting of major depression, dysthymia and/or intermittent anxiety is predictable. Results have been presented in a number of subjects. There is no basis for the assertion that the effects would be different in subjects without frown or glabellar lines, as discussed below. Results obtained using the claimed methods are presented in the specification, and additional results are presented in the Declaration submitted herewith.

(7) The quantity of experimentation required

Limited, if any experimentation would be required to practice the claimed methods of treatment.

(8) The presence of working example

A number of working examples has been provided. Evidence was previously presented documenting that the claimed methods are effective in subjects that have frown and glabellar lines. This evidence was acknowledged in the Office action. In addition, the Declaration submitted herewith provides additional evidence that documents that the claimed methods work in subject without frown and/or glabellar

lines. Thus, the presently claimed methods are effective for subjects with or without frown or glabellar lines.

Thus, the claimed methods are fully enabled by the specification, as supported by the above analysis and the data of record. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

Applicants believe that the present claims are in condition for allowance, which action is requested. *If any issues remain prior to allowance, the Examiner is formally requested to contact the undersigned prior to issuance of the next Office action, in order to arrange a telephonic interview.* It is believed that a brief discussion of the merits of the present application may expedite prosecution. This request is being submitted under MPEP §713.01, which indicates that an interview may be arranged in advance by a written request. In view of the nature of the rejections, Applicants also expressly reserve the right to file an Appeal.

Respectfully submitted,

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